RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Medications That Normalize Brain Glutamate Reduce Drug-Seeking in Rats

A compound used to treat pulmonary disease has a long-lasting impact on heroin-seeking.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Two recent NIDA-funded studies demonstrate the promise of treating addiction with medications that alleviate drug-induced alterations in signaling by the neurotransmitter glutamate. In the studies, rats treated with acetylcysteine or ceftriaxone exhibited reductions in behaviors that correspond to human relapse to cocaine and heroin abuse.

Acetylcysteine is currently prescribed to treat pulmonary disease and acetaminophen overdose, and ceftriaxone is prescribed as an antibiotic. Because their safety has been established in clinical use, addiction researchers have been able to move quickly to clinical trials. A large-scale trial with acetylcysteine is already under way.

SIGNAL DISRUPTION

Dr. Peter Kalivas and colleagues at the Medical University of South Carolina (MUSC) conducted the new studies. They had previously demonstrated that changes in brain glutamate signaling induced by chronic drug exposure have a wide variety of neurobiological effects that appear to be instrumental in the transition from occasional drug abuse to addiction (see box, page 14).

In recent work, the researchers discovered the molecular mechanism by which drugs of abuse disrupt glutamate signaling. Chronic exposure sharply reduces levels of two proteins that control the movement of glutamate into and out of non-neuronal cells called glia. Normally, the reciprocal activities of these proteins—the glial-glutamate transporter-1 (GLT-1) and the cystine-glutamate exchanger (xCT)—maintain an appropriate balance between freely circulating extracellular glutamate and glutamate sequestered inside glia. When chronic drug exposure renders GLT-1 and xCT scarce, the supply of extracellular glutamate available for neurons to use as signal molecules is diminished.

Chronic drug exposure sharply reduces levels of two proteins that control the movement of glutamate.

Having mapped this mechanism, the researchers identified acetylcysteine as a medication that raises the brain's production of xCT and therefore might help restore glutamate balance. Research by others suggested that ceftriaxone increases levels of GLT-1.

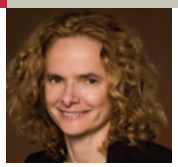
LEVERS AND LEARNING

Dr. Kalivas and colleagues tested the medications using an animal behavioral protocol that

[*Continued on page 13*]

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*



New Tools and Strategies to Bolster Behavioral Therapy

Through skillfully administered behavioral therapy, recovering drug abusers can learn to resist cravings and avoid situations that trigger relapse. Many long-term abusers, however, experience memory and cognition impairments that impede their progress in this life-saving educational process. To remedy this problem, NIDA-funded scientists are investigating whether certain medications might strengthen patients' understanding and memory retention. They are also studying the potential of computers and other technologies to extend the reach of therapy and improve followup care.

The principle of using medication to enhance behavioral therapy has already shown promise in several nondrug contexts, including, for example, the treatment of patients with a morbid fear of heights. In a preliminary trial, 60 percent of patients who received D-cycloserine (DCS) prior to two behavioral therapy sessions reported that they were "much improved" when fear of heights was assessed 1 week and 3 months after treatment; only 20 percent of patients given a placebo reported such progress. DCS has also shown positive results in people with social anxiety and obsessive-compulsive disorder.

NIDA-supported investigators are initially focusing on cognitive enhancers to help people quit methamphetamine and other stimulants, drugs that cause some of the most debilitating cognitive impairments during early abstinence. One medication currently under study is modafinil, a mild stimulant that appears to have positive effects on executive function—planning, setting goals, regulating behavior—and impulsivity. The study will measure whether modafinil helps patients progress in cognitive-behavioral therapy (CBT). Researchers suggest that cognition-enhancing medications might permit clinicians to reduce the number of CBT sessions required to counter addiction and thereby reach more people in need of therapy.

Technology—computer software, Web sites, even telephones—may enhance the potency, reach, and cost-effectiveness of behavioral treatment. Patients who cannot or will not attend live therapy sessions may benefit from computer software designed to teach relapse-avoidance skills. Similarly, booster sessions delivered via telephone or the Web might reinforce abstinence. Some providers may offer in-person treatment sessions early in a patient's therapy and then shift to telephone or computer delivery of treatment. These technologies should be particularly beneficial for patients who live in remote areas or have limited mobility.

Cognitive enhancers and computers have great potential to augment patients' acquisition of behavioral therapy's skills and lessons. Technology also promises to provide therapists with new, cost-effective tools to help their patients maintain behavioral changes they achieve during treatment. NIDA is committed to ushering these innovative approaches smoothly and efficiently through the stages of discovery and into the Nation's clinics. ■

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High, Persistent Rates of Risky Sexual Behaviors in Delinquent Youth

Young people who have gotten into trouble with the criminal justice system report high rates of sexual behaviors that increase risk of HIV and other sexually transmitted infections (STIs).

Dr. Linda A. Teplin, principal investigator, Dr. Katherine S. Elkington, and colleagues at Northwestern University conducted a longitudinal study of 689 boys and girls aged 10 to 18 in Chicago's Cook County Juvenile Temporary Detention Center. The researchers found that all the delinquent youth were at high risk for HIV and other STIs but that substance use disorder greatly increased the risk.

When asked about the previous 3 months, 25 percent of the study participants reported unprotected sex, and more than 40 percent said they had sex while drunk or high. Three years later, the prevalence of risky sexual behaviors had increased: 50 percent reported unprotected sex during the previous 3 months and more than 60 percent reported sex while drunk or high. Youth with a substance use disorder at the initial interview were the most sexually active and showed the highest incidence of risky sexual behaviors at the followup interview: 75 percent of these young people engaged in five or more risky sexual behaviors. In contrast, among those with a serious mental disorder—such as a major depressive disorder, manic episode, or psychosis—without substance abuse, 50 percent engaged in five or more risky sexual behaviors. This group had the lowest risk of unprotected sex among those studied. The researchers recommend that health care and juvenile justice professionals collaborate to develop effective HIV/STI interventions that can begin in detention centers, where youths typically stay 2 weeks, and continue after release.

> Journal of the American Academy of Child and Adolescent Psychiatry 47(8):901-911, 2008.

Brain Opioid Receptor Levels Predict Time to Cocaine Relapse

Cocaine abusers who maintain high levels of the μ-opioid receptor in their brain during early abstinence relapse sooner than abusers whose levels drop. Dr. J. James Frost of the Johns Hopkins University School of Medicine and Dr. David A. Gorelick of NIDA's Intramural Research Program (IRP) and colleagues used positron emission tomography and a radiotracer ([^{11}C]carfentanil) to measure μ-opioid receptor levels in 15 cocaine abusers who agreed, for a fee, to stop taking the drug and live in a supervised clinical research facility for 3 months. After discharge, the participants reported on their drug use and submitted periodic urine samples for a year.

During the 3 months of monitored cocaine abstinence at the research facility, μ-opioid receptor levels decreased in the frontal and temporal regions of the cortex. Participants who showed lesser decreases during this period tended to experience earlier relapse—as defined by two consecutive days of cocaine use—after leaving the facility. Higher μ-opioid receptor levels at the time of leaving were also associated with more days of cocaine use in the first month following a relapse.

In a study conducted with IRP colleagues Drs. Udi Ghitza and Kenzie Preston, the research team reported similar findings among a group of cocaine abusers participating in 12 weeks of medication-free psychosocial outpatient treatment. The researchers suggest that receptor levels may influence relapse by mediating craving.

> Biological Psychiatry [Epub ahead of print, June 24, 2010] Psychopharmacology 200(4):475-486, 2008.

Lower Levels of Dopamine-Regulating Receptors Among Novelty Seekers

New experiences trigger a spurt of dopamine from the midbrain, but some individuals react more strongly than others do. Researchers at Vanderbilt University have identified a cellular mechanism that might underlie these differences.

Dr. David H. Zald and colleagues report that people who have a tendency to favor novelty have lower-than-average availability of a receptor that inhibits dopamine's release from neurons. Lower receptor availability translates into heightened dopamine release, which likely stimulates the activity of reward circuits, the researchers say.

The team ranked 34 study participants, aged 18 to 38, on the basis of novelty-seeking personality traits, which include impulsiveness, willingness to spend money freely, and a preference for spontaneous action. Using positron emission tomography imaging with the radiochemical [18F] fallypride, Dr. Zald and colleagues found a strong link between novelty-seeking behavior and low dopamine receptor availability in the midbrain, which includes sections of the pathways that influence reward and movement.

The findings accord well with the results of previous animal studies and suggest that the availability of dopamine-regulating receptors in midbrain neurons may partly determine responsiveness to novelty and other rewards.

> The Journal of Neuroscience 28(53):14372-14378, 2008.

Neuroimaging Challenges Common Assumption of Public Service Messaging

Study suggests a role for the technology in designing effective media strategies.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Televised public service announcements (PSAs) with frequent cuts, bright colors, loud music, and surprising visual images may grab the eye and ear, but are they more likely than other ads to spur viewers to act on their messages? A NIDA-funded study that recorded smokers' brain function while they watched antismoking PSAs suggests that calmer ads may be more effective. Although the researchers did not track whether any smokers quit, they found that low-key ads connected better with some brain regions that would be likely to support efforts to abstain.

THIS IS YOUR BRAIN ON ADS

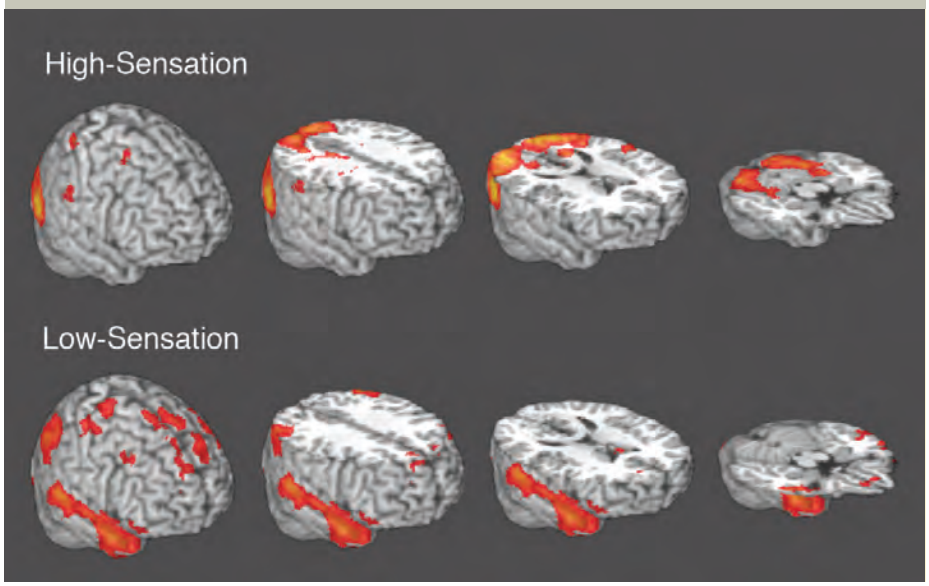
Many creators of PSAs suppose that seizing and holding viewers' attention are prerequisites for driving messages home and that highly affective and sensationalistic ads do this best. Recently, however, some theorists have suggested that although viewers cannot take their eyes away from such ads, their ability to absorb and utilize the messages the ads promote may be limited. According to this theory, which has some support in behavioral studies, the brain has only so much capacity to process incoming impressions, so that the more it expends upon the sensational aspects of an ad, the less it has available to process the ad's meaning.

Dr. Daniel Langleben and colleagues at the University of Pennsylvania, collaborating with media expert Dr. Joseph N. Cappella of Penn's Annenberg School for Communication, brought brain imaging to bear on the issue. Their study is the first to monitor individuals' brain responses as they watched antismoking ads in their entirety. "A PSA delivers a coherent message as well as a visual presentation, and scientists need to determine how the brain responds to an ad as a whole," says Dr. Langleben.

The researchers showed 18 smokers, aged 18 to 48, a series of 30-second video clips. From 99 antismoking ads produced before 2002, eight clips were drawn: the four that had been rated "highest sensation" and the four that had been rated "lowest sensation." The sensation ratings had been made using a standard procedure that took into account visual and audio elements and emotional impact. The clips were shown in random order along with eight clips from a wildlife documentary. While participants watched the videos, they underwent functional magnetic resonance imaging.

Both types of PSAs generated more overall brain activity than the wildlife clips, presumably because their content was more relevant to the audience. High-sensation PSAs stimulated activity primarily in the occipital cortex, an area at

DIFFERENT BRAIN RESPONSES Antismoking public service announcements (PSAs) with colorful images, frequent cuts, and dramatic narration generated greater brain activity (indicated by red and orange) than low-sensation ads in visual-processing brain regions at the back of the brain (images, top row). However, low-sensation PSAs provided greater stimulation of memory and attention areas toward the front and on the side (images, bottom row). The back of the brain is on the left side of the images. The illustration shows, from left to right, successively deeper slices through the brain.



the back of the brain that processes visual information. The low-sensation PSAs, in contrast, had the largest impact on the prefrontal and temporal cortices, regions associated with attention, memory, and speech processing.

Beginning 5 minutes after the last video clip ended, the participants viewed 128 still frames in random order; 64 were from the PSAs and wildlife clips shown previously, and 64 were from other antismoking and nature videos. After a 3-second presentation of each frame, the participants reported whether they had just seen an ad with this image. They recognized 88 percent of the frames from the low-sensation PSAs as compared with 78 percent of the high-sensation ones. They also were quicker to recognize frames from the low-key PSAs.

STUDY TESTS OPPOSITE TYPES OF ADS Televised public service announcements (PSAs) can promote important public health messages, including smoking cessation and drug abuse prevention. But what is the best way to convey those messages—with an eye-catching, flashy presentation or a low-key, didactic ad? Dr. Daniel Langleben and colleagues examined brain responses to both types of ads:

In a high-sensation PSA called "Outside the Bar" (above), an attractive woman tells a smoker he is not welcome at the gathering. The ad is vibrant and visually appealing—with music, bright color, and frequent cuts.

In a low-sensation PSA called "Stealing" (above), a young man says that he used to steal cigarettes from his parents just as they had done from their parents. "Now, I have spots on my lungs because of smoking," he concludes. The ad is calm and shifts scenes rarely.

Stronger activation in the attention and memory areas of the brain corresponded with greater accuracy on the recognition test, whereas stronger activation in the visual-processing area was associated with lower scores on this test. The results suggest that the frequent cuts, bright colors, and other high-sensation effects may impede PSAs from lodging in memory.

Dr. Langleben cautions that, in contrast to seeing PSAs outside an experimental setting, his study participants' attention to the ads was guaranteed. He also notes that ads did not vary in strength of argument—how convincingly the case for quitting was made—as evaluated by participants in a separate study. Nevertheless, he affirms, "Our findings cast doubt on the premise that flashier ads are always more effective."

A NEW TOOL

Noting that the PSAs shown in the study represented the top and bottom 25 percent of the ads' sensation values, Dr. Langleben adds, "A key goal for future neuroimaging research will be to determine the optimal balance of attention-attracting and message-conveying elements for PSAs." The researchers would also like to examine how initial brain processing of PSAs influences long-term memory for the ads.

"These findings give scientists a basis for examining brain responses to PSAs among important target audiences for these ads—children and adolescents, for example," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research. He notes that high-sensation ads may generate different brain responses—and therefore better attention and memory—among particular groups of people.

One goal of a follow-up study by Dr. Langleben's team is to determine whether participants who are strongly drawn to sensory experiences process PSAs differently than those without this disposition. The team will also examine the interplay between an ad's strength of argument and its graphic attractiveness.

With further testing, health promotion experts may add neuroimaging to their toolbox for PSA development. Dr. Grant says, "Media experts have been arguing about the elements of effective ads for years. This study shows that researchers can use neuroimaging to test competing hypotheses, models, and theories in health communication and marketing." ■

SOURCE

Langleben, D.D., et al. Reduced prefrontal and temporal processing and recall of high "sensation value" ads. *NeuroImage* 46(1):219-225, 2009.

Crack Cocaine Promotes Progression of HIV Infection to AIDS

Cellular studies of cocaine and methamphetamine offer clues to underlying mechanism.

BY SHARON REYNOLDS,
NIDA Notes Contributing Writer

Human immunodeficiency virus (HIV) inflicts disproportionate suffering on drug abusers. They have an extremely high prevalence of infection because the virus transmits easily via shared drug-injection equipment and through drug-influenced risky sexual behavior. They progress to disability and death more rapidly because diagnosis and treatment are often delayed and their lifestyle and circumstances limit their ability to adhere to demanding antiretroviral medication regimens.

And that's not all, according to two recent studies by NIDA-funded investigators. One found that crack cocaine users who are infected with HIV experience an accelerated decline in immune function that is independent of their adherence to therapy. In the other, cocaine and methamphetamine increased both the ease with which the HIV virus entered immune cells in laboratory cultures and its replication rate once inside the cells.

ACCELERATING THE DEVELOPMENT OF AIDS

Dr. Marianna Baum and colleagues at Florida International University followed 222 HIV-positive drug abusers in Miami for 30 months. Each month, the participants reported on their drug and medication use, and they gave blood samples every 6 months to be assayed for levels of the virus and of the immune cell, CD4, that the virus primarily attacks. At each visit, the participants were designated as crack cocaine users or nonusers, depending on whether they reported taking the drug at any time during the previous 6 months. When the data were analyzed, they showed an association between crack cocaine use and more plentiful virus in users' blood that was independent of their degree of antiretroviral adherence. There were no significant differences in viral load associated with use of powdered cocaine, marijuana, or alcohol.

The data showed an association between crack cocaine use and more plentiful virus in users' blood that was independent of their degree of antiretroviral adherence.

To investigate disease development, the researchers focused on the 130 participants who, at the start of the study, had more than 200 CD4 cells per microliter (µL) of blood. Among that group, use of crack cocaine more than doubled the likelihood of a participant's CD4 cell count dropping below that level—and thus meeting the criterion for an AIDS diagnosis—during the study. Dr. Baum and colleagues did not observe any changes in disease progression related to the use of powdered cocaine, marijuana, or alcohol.

To determine whether crack cocaine had an effect on HIV progression independent of its influence on adherence to HIV treatment, the researchers separately analyzed the data for the 53 participants with more than 200 CD4 cells/µL at baseline who were not taking antiretroviral drugs. Of the crack cocaine users in this group, 51 percent dropped below 200 CD4 cells/µL during the 30-month followup, compared with 13 percent of the nonusers of the drug. Dr. Baum says, "The results indicate that, in addition to reducing treatment adherence, crack cocaine increases the risk of progression to AIDS by accelerating the decline of the CD4 cell count."

In keeping with previous studies, the team also found that use of crack cocaine, but not the other drugs, reduced the success of antiviral medications. At the start of the study, among participants receiving antiretroviral therapy, 39 percent of nonusers of crack cocaine, as compared with 27 percent of users, had fewer than 400 copies of the virus per milliliter of blood, which is considered a sign that the antiviral regimen is working well. Moreover, the percentage of nonusers meeting this criterion was the same at the 12-month followup assessment, while the percentage of crack cocaine users who had fewer than 400 copies per milliliter had fallen from 27 to 15 percent.

Though the researchers are not sure why crack cocaine was the only drug among those studied to affect HIV progression independent of treatment adherence, Dr. Baum speculates that "it may be associated with the frequency of use. Crack cocaine is relatively inexpensive—around $3 to $5 per dose—and it can be bought easily on the street. The other drugs studied are more expensive than crack cocaine," and thus are used less frequently in the population studied, she says. Dr. Baum notes that frequent use of

crack cocaine places socioeconomic pressures on the user, reducing the proportion of income used for medical care and food. Crack cocaine also decreases appetite and is associated with nutritional deficits that impair the immune system.

Dr. Baum notes that the new findings highlight the quest for better-targeted interventions to help HIV-infected patients quit illicit drug use: "We need to get these patients into drug treatment, not only because drug use affects adherence to HIV medications, but because we now know that drug abuse impacts disease progression itself."

HELPING HIV ENTER CELLS

If crack cocaine drives HIV progression, how does it do so? Dr. Madhavan Nair of Florida International University suggests that the answer is, in part, that cocaine abets the virus' insidious strategy for attacking the immune system.

Dr. Nair and colleagues have been studying HIV's interaction with the first cells it encounters in the immune system. These cells, called dendritic cells, patrol the blood and tissues for potential pathogens. When a dendritic cell encounters viruses or bacteria, it binds them to receptors on its surface, draws them inside itself, and then alerts other immune cells to the presence of the pathogen.

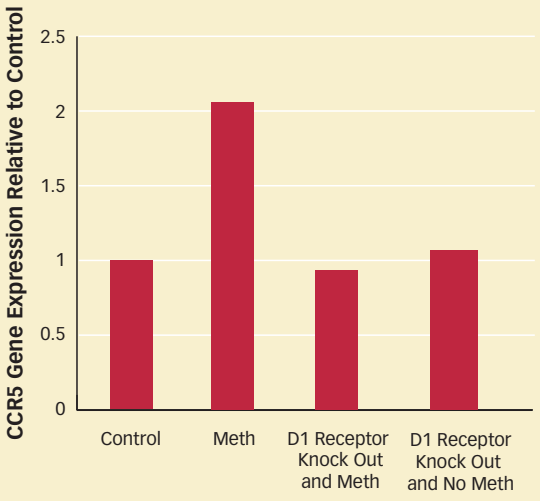
Previous investigations have shown that HIV takes advantage of this system. It attaches to the dendritic surface receptors, rides the dendritic cells until they contact other cells, and then attacks those other cells. By weakening and destroying the additional cells—and CD4 cells, in particular—the virus cripples the body's ability to ward off subsequent viral and bacterial invaders.

Dr. Nair and colleagues examined dendritic cells and their components in blood from HIV-infected and uninfected individuals, including people who did and who did not use cocaine. The team found that cocaine increases production of one of the receptors, called DC-SIGN, that dendritic cells use to capture invading organisms. As a result, when the invading organism is HIV, dendritic cells pick up and deliver more of the virus, enhancing its spread to the CD4 and other cells with which they come in contact. Moreover, Dr. Nair found that cocaine increases the rate of replication of HIV within dendritic cells, increasing still further the virus' spread to other immune-system cells and contributing to the demise of dendritic cells.

Dr. Nair's team recently demonstrated that methamphetamine, like cocaine, stimulates production of receptors that draw HIV into dendritic cells. Using cell cultures, they documented that dendritic cells exposed to methamphetamine generated more than twice as many CXCR4 and CCR5 receptors within 24 hours, compared with unexposed cells. The percentage of methamphetamine-exposed cells infected with HIV was sevenfold that of control cells, and the viral replication rate inside them was 57 percent higher.

The initial mechanism of stimulant-induced dendritic cell receptor production appears to be the same as that underlying these drugs' psychoactive effects: hyperactivation of the dopamine neurotransmitter system. When the researchers treated drug-exposed, HIV-infected cell cultures with a chemical that prevents dopamine from influencing dendritic cells, the increase in dendritic cell receptors was suppressed.

HOW METHAMPHETAMINE INCREASES HIV REPLICATION When dendritic cells in laboratory culture were exposed to methamphetamine, activity increased in the gene for a receptor, CCR5, that the virus exploits to enter cells. Knocking out production of the D1 receptor prevented methamphetamine from producing this effect.



IMPLICATIONS FOR TREATMENT

Dr. Nair says that learning the details of how dendritic cells interact with HIV and pass it on to other immune cells can provide a basis for effective new HIV treatment approaches. "Even with antiretroviral therapy, you cannot eliminate the HIV virus from the body," says Dr. Nair. "But if we could affect some of these specific receptors, we might be able to block the virus from entering the cells."

Dr. Jag Khalsa, chief of NIDA's Medical Consequences Branch, says, "Now that we understand this mechanism, we can try to develop drugs that target the receptors—blocking them so that methamphetamine or cocaine has no effect. NIDA is now funding research in this area." ■

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Nair, M.P.N., et al. Methamphetamine enhances HIV-1 infectivity in monocyte derived dendritic cells. *Journal of Neuroimmune Pharmacology* 4:129-139, 2009.

School-Wide Program Reduces Problem Behaviors and Improves Academic Outcomes

Positive Action schools, families, and communities emphasize fairness and respect.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Positive Action, a school-centered program for social and emotional development for grades 1 to 12, was credited with a sharp reduction in rates of substance abuse, violent behavior, and voluntary sexual activity among primary school children in a recent NIDA-funded study. Hawaiian-fifth graders who had participated in the program for 3 or 4 years self-reported most of these problem behaviors half as frequently, or less, compared with peers who were not exposed to it. Lead investigator Dr. Brian Flay of Oregon State University notes that behavioral problems increase sharply after fifth grade; if the observed reductions carry into later ages, the benefit to students, their families, and their communities will be great.

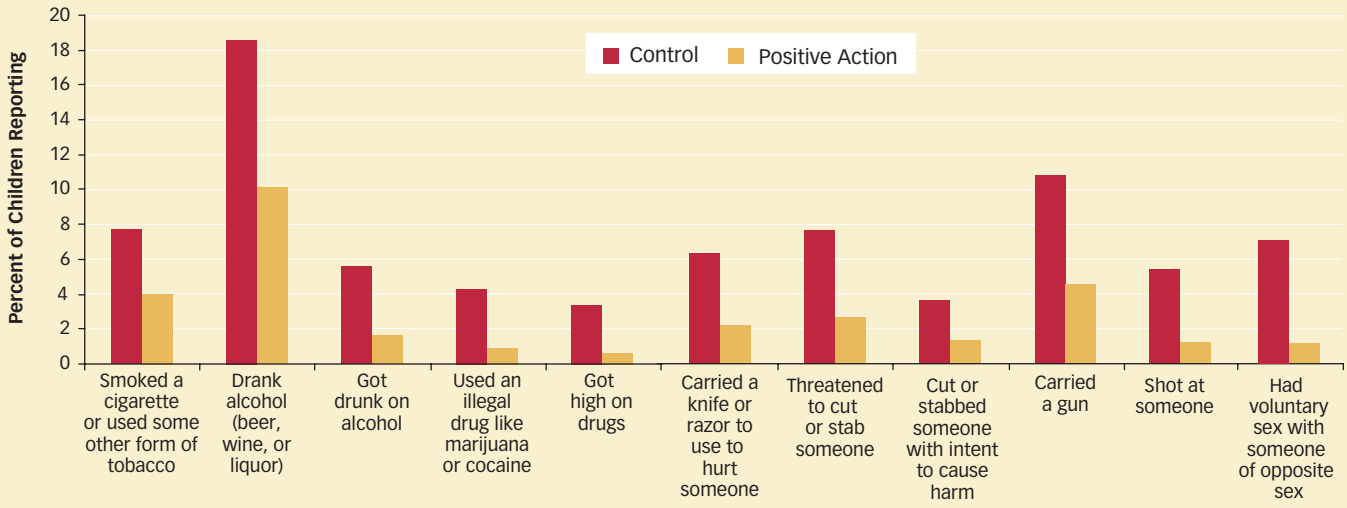
DO GOOD, FEEL GOOD

Teachers are the central actors in Positive Action. In 140 lessons—roughly 35 hours of instruction—per academic year, they cover a curriculum based on a simple core philosophy: "You feel good about yourself when you do positive actions; you feel bad about yourself when you do negative actions." Each lesson encourages healthy behavior and academic achievement through specific positive acts—for example, eating good food, doing homework, reading for fun, sleeping regularly, not consuming harmful substances, getting along with others, and developing self-control. At any given time, teachers of every grade focus on the same topic at age-appropriate levels to reinforce and solidify concepts throughout the school.

School principals and counselors, family members, and community leaders also have roles in Positive Action, ensuring that school, home, and community climates reflect the program's aims.

Complete program materials for all these groups cost approximately $450 per classroom, excluding teacher training (*www.positiveaction.net*).

PREVENTION PROGRAM REDUCES UNHEALTHY BEHAVIORS Fifth-graders whose schools participated in Positive Action for more than 3 years early in elementary school reported lower rates of substance abuse, violence, and voluntary sexual behavior than children in control schools.



POSITIVE ACTION VERSUS BUSINESS AS USUAL

The 1,714 boys and girls who reported their experiences in the recent study were ethnically diverse, and the mix was similar to that of the state, with the majority being of Hawaiian, Asian, or multiple ethnicities. Participants attended 20 public elementary schools in which at least one-quarter of students received free or reduced-price lunches, and academic achievement levels were moderate to low compared with the average of Hawaiian schools. The researchers divided the schools into 10 pairs, each of which was closely matched based on a lengthy list of characteristics that might influence rates of problem behaviors. One school in each pair was randomly assigned to implement Positive Action, the other to carry on as usual.

The fifth-graders' self-reports indicated that most of the problem behaviors were uncommon, as would be expected among children so young. However, the intervention group had lower levels than the control group among all the behaviors except for a few in which there was no measurable difference. The most widely acknowledged problem behavior was drinking alcohol (10 percent among Positive Action participants, 19 percent among controls), and the least reported was getting high on drugs (0.7 percent Positive Action participants, 3.5 percent controls).

The teachers of the Positive Action recipients reported significantly fewer behavioral problems among their students than teachers of control children did among theirs; however, differences between teacher reports were smaller than those between student self-reports.

Dr. Flay says that the findings substantiate favorable results from a concurrent study of Positive Action in Chicago public schools. They also are consonant with studies that have shown similar benefits from other programs that share the strategy of inculcating healthy habits in early childhood to prevent problems throughout individuals' development ("Behavior Game Played in Primary Grades Reduces Later Drug-Related Problems," *NIDA Notes* Volume 23, Number 1). Moreover, the benefits of such programs may endure into the critical teenage years. Dr. Flay and colleagues have found that among middle and high schools in another region of the country, the higher the percentage of students completing the Positive Action program, the lower student smoking rates.

OTHER OUTCOMES

One year after the study, Positive Action schools demonstrated improved standardized test scores for reading and math compared with the year prior to program implementation. For example, fifth-graders at intervention schools scored about 10 percent higher in reading and about 9 percent higher in math on the TerraNova test (2nd edition). Analyses of administrative data before and after program implementation indicated that Positive Action schools lowered absenteeism by about 15 percent, reduced suspensions by 73 percent, and held students back a grade 73 percent less often.

"Children hear many mixed messages about what is appropriate and often do not know positive behaviors when they enter school," says Dr. Flay. "Through Positive Action, adults can teach and instill motivation for pro-social behaviors and encourage healthy emotional responses. In this way, the program reduces a range of problem behaviors by offsetting broader dysfunction in classrooms, schools, and communities," says Dr. Flay.

"The advantages conferred by Positive Action and other early skill-development programs are exciting to see," says Dr. Aria Crump of NIDA's Division of Epidemiology, Services and Prevention Research. "Also, the fact that this intervention has been tested with diverse populations provides support for the generalizability of this approach." ■

"WHEN YOU DO GOOD, YOU FEEL GOOD" The thoughts-actions-feelings cycle that is shown on posters and stickers reminds children of the Positive Action program's central idea. Six units each focus on a specific theme.

- Developing self-concept: What it is, how it's formed, and why it's important (philosophy and thoughts-actions-feelings circle)
- Maintaining a healthy body and mind (includes motivation to learn)
- Managing yourself responsibly (self-control skills)
- Getting along with others by treating them the way you like to be treated (social-emotional skills and character)
- Being honest with yourself and others (mental health)
- Improving yourself continually (setting and achieving goals)

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Brain Adaptation May Dampen Effects of Cocaine

Dendritic spine proliferation seems to compensate for some impacts of cocaine use.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

NIDA-funded researchers recently were surprised to find evidence that a cocaine-induced change in the structure of brain cells represents an adaptive response that may limit the drug's impact. Previously, scientists had suspected the opposite—that the modification contributed to the tenacity of some harmful effects.

Cocaine's acute psychoactive effects, such as the rush and high, occur because the drug disrupts the normal ebb and flow of neurotransmitter molecules that carry signals between brain cells. The drug's mechanisms for producing longer-lasting effects, such as craving and altered decisionmaking, are unknown. However, because those long-lasting effects persist after the drug leaves the brain, scientists have inferred that alterations of the brain cell structures that receive and process neurotransmitter signals might be involved.

A leading hypothesis has proposed that a structural change that accounts for cocaine's long-lasting effects is drug-induced proliferation of dendritic spines on neurons in the nucleus accumbens (NAc), a brain region involved in reward, motivation, and addiction. Increases in numbers of these knobby, neuroreceptor-rich structures accompany the development of cocaine addiction (see figure, right). New dendritic spines could render neurons more responsive to neurotransmitter stimulation and theoretically might form novel, overriding, semipermanent signaling pathways that could underlie persistent drug-related behaviors.

In a series of experiments with laboratory animals, Dr. Christopher W. Cowan and colleagues at the University of Texas Southwestern Medical School set out to determine cocaine's mechanism for increasing the number of dendritic spines and to test the dendritic spine hypothesis. Their unexpected result suggests that scientists will need to look elsewhere for an explanation of cocaine's persistent effects.

The work also revealed cocaine's mechanism for increasing dendritic spines, and that finding suggested a potential new medication strategy for treating cocaine addiction.

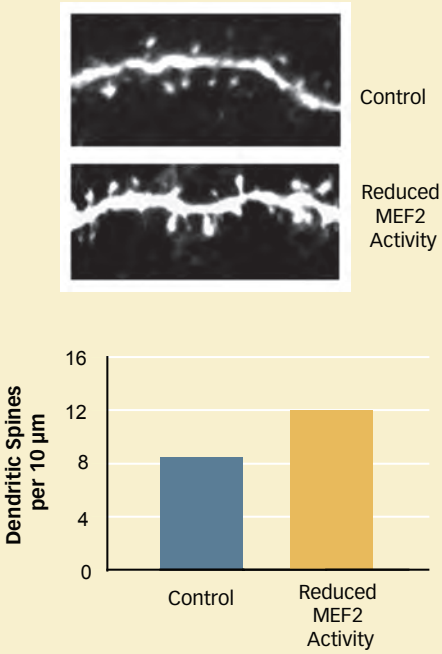
REVEALING THE MECHANISM

The Texas team's investigations centered on a small family of proteins, myocyte enhancer factor 2 (MEF2), whose many functions include regulating the number of excitatory synaptic connections in the brain. Consistent with this role, several studies have shown that in some parts of the brain, the number of dendritic spines—which are sites of excitatory synapses—is inversely related to levels of MEF2 activity.

Other studies have shown that cocaine increases the activity of an enzyme, cyclin-dependent kinase 5 (Cdk5), that inhibits MEF2 activity. Accordingly, Dr. Cowan says, "We hypothesized that chronic exposure to cocaine would inhibit MEF2, which would lead to an increase in the number of dendritic spines and alter behavioral responses to repeated cocaine use."

In an initial set of experiments, Dr. Cowan and colleagues confirmed that cocaine reduces MEF2 activity in the NAc, and they mapped out the underlying molecular pathways (see box, page 11). They then established that MEF2 inhibition is the link between cocaine and dendritic spine proliferation by demonstrating that:

BLOCKING MEF2 INCREASES THE PROLIFERATION OF DENDRITIC SPINES RNA interference sequences that reduce production of MEF2 proteins result in more dendritic spines (the knoblike projections in the micrographs) along neurons of the nucleus accumbens.



Graph and photograph from *Neuron* 59(4); Copyright Elsevier, 2008.

Scientists Reveal Biochemical Underpinnings of Cocaine Effects

The molecular events that link cocaine and behavioral changes that the drug engenders involve the protein family called myocyte enhancer factor 2 (MEF2) and the production of knobby, receptor-rich structures called dendritic spines. To date, Dr. Christopher W. Cowan and his team at the University of Texas Southwestern Medical School have identified the following biochemical ties:

- *Two ways in which cocaine reduces MEF2 activity in the nucleus accumbens (NAc)*. First, chronic cocaine exposure boosts the activity of an enzyme, called cyclin-dependent kinase 5, that adds phosphate groups to MEF2 proteins. This phosphorylation inactivates the proteins, which regulate the activity of various genes. Second, cocaine increases the abundance of dopamine. Dr. Cowan and his team have found that when dopamine binds to the dopamine-1 receptor, it inhibits the activity of an enzyme, called calcineurin, that removes phosphate from MEF2 molecules. More phosphate groups remain attached to MEF2 proteins, thereby lowering their activity.

- *Eighty-two genes that cocaine may inhibit by suppressing MEF2 activity*. Each of these genes was found to be associated with MEF2 and so may regulate the number of dendritic spines. The proteins encoded by these genes can now be investigated to see whether reducing their abundance increases dendritic spine density or other cocaine effects. Some of these proteins have already been linked to cocaine's effects in other studies. One, for example, influences the activity of an enzyme linked to locomotor responses affected by cocaine.

- In and of itself, reducing MEF2 activity in the NAc resulted in an increase in the number of dendritic spines there;
- If cocaine is prevented from inhibiting MEF2 activity, it does not increase dendritic spines.

For the first demonstration, the researchers gave mice two injections, one into each side of the NAc. One of the injections contained virus into which the researchers had incorporated two RNA interference (RNAi) sequences that together shut down most MEF2 activity; the other, a control injection, contained a similar RNAi sequence that had been modified so that it would not affect MEF2. The researchers then gave some of the animals cocaine and the others saline daily for 4 weeks, then counted dendritic spines. The cocaine-treated animals had more spines than the saline-treated animals on the side of the NAc with normal MEF2 activity, but on the side with reduced MEF2 activity, cocaine did not cause spine proliferation beyond that observed in the saline-treated animals.

For the second demonstration, the researchers repeated the previous procedures with different viruses. This time, the experimental virus led to MEF2 activity that was resistant to inhibition by Cdk5. As anticipated, cocaine given daily for 4 weeks did not result in greater dendritic spine proliferation than saline on this side of the NAc, indicating that inhibition of MEF2 is needed for cocaine-induced spine changes to occur.

A SURPRISING FINDING

Satisfied that cocaine causes dendritic spine proliferation by inhibiting MEF2, Dr. Cowan and colleagues addressed the hypothesis that links an increase in dendritic spines to the behavioral effects of cocaine. Experimental mice were injected with the inhibition-resistant form of MEF2 proteins into the NAc on both sides of the brain. Since under these conditions, cocaine is prevented from inhibiting MEF2 and does not produce additional dendritic spines, the scientists did not expect the mice to exhibit behaviors associated with cocaine dependence, such as preference for a place where the drug had been administered and high locomotor activity in response to repeated doses of cocaine.

But the opposite occurred. Compared with control animals with normal MEF2, the treated mice showed a more pronounced locomotor response to cocaine and increased preference for a chamber

where they had previously received the drug. "I was as surprised as anyone by our finding," Dr. Cowan says. At the very least, he adds, the findings show that increases in dendritic spine density and behavioral sensitization to cocaine are "functionally uncoupled—you can block the spine increase and still get the behavioral changes." Beyond that, the results suggest that dendritic proliferation in the NAc may represent an adaptation that limits the effects of cocaine. In the absence of dendritic spine growth, Dr. Cowan notes, the cocaine-sensitized behaviors did not simply remain the same—they increased.

The production of dendritic spines, Dr. Cowan suggests, might be the brain's attempt to rebalance a system that cocaine has thrown off kilter. The NAc neurons that his team examined receive excitatory signals primarily from the prefrontal cortex, where activity is suppressed by repeated cocaine use in both humans and rodents. Dendritic spine proliferation could help offset the impact of reduced NAc activity by amplifying the weakened signals.

Dr. Jonathan Pollock, chief of the Genetics and Molecular Neurobiology Research Branch at NIDA, agrees that the increase in dendritic spine density "looks like a compensatory mechanism that dampens the effects of cocaine." The findings, he says, "raise the larger question of how synapses are strengthened or weakened in response to drugs."

By exploring the influence of MEF2 on dendritic spines, scientists might unveil potential targets for therapy, Dr. Pollock notes. If further research confirms that MEF2 inhibition blocks the effect of cocaine, pharmacologists could use this action as a criterion when screening compounds for potential antidrug activity.

The findings suggest "new directions for looking at synaptic adaptability and hints of how we can manipulate the process environmentally or chemically," Dr. Pollock adds. ■

SOURCE

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MEDICATIONS

[*Continued from page 1*]

simulates human relapse to addiction. To begin, they trained rats to press a lever to self-administer heroin or cocaine. Once the animals became steady drug takers, after about 2 weeks, the researchers deactivated the lever. Over the next 15 days in the heroin experiment (21 days in the cocaine experiment), the animals reduced the frequency with which they pressed the lever, which no longer delivered a reward. On the 16th day (22nd in the cocaine experiment), the researchers showed the animals a cue that had previously signaled drug availability. All the animals reverted to lever pressing, a response that parallels human cue-induced relapse to drug abuse.

To assess the medications' effects on drug-seeking, the researchers treated some rats in the heroin experiment with acetylcysteine, some rats in the cocaine experiment with ceftriaxone, and others with an inert substance. Each medication or inert substance was injected daily for 5 to 15 days starting on the day the lever was deactivated. The results showed that:

- The rats that received acetylcysteine learned that the lever no longer delivered heroin more quickly than the control rats. The difference was particularly striking during the first 5 days following deactivation.
- Rats that received either medication pressed the lever less often than the control animals in response to a cue or a low-dose priming injection of drug (see graph, right).
- The rats that received acetylcysteine also pressed the lever less often than control rats when retested 40 days after lever deactivation.

"The team's finding that acetylcysteine can attenuate rodents' drug-seeking for longer than a month is unique and astounding," says Dr. Nancy Pilotte of NIDA's Division of Basic Neuroscience and Behavioral Research.

"Our results suggest that acetylcysteine may help abstinent substance abusers learn lessons from behavioral therapy more easily, as well as prevent them from relapsing. This would be a powerful double benefit for these patients," says Dr. Kalivas.

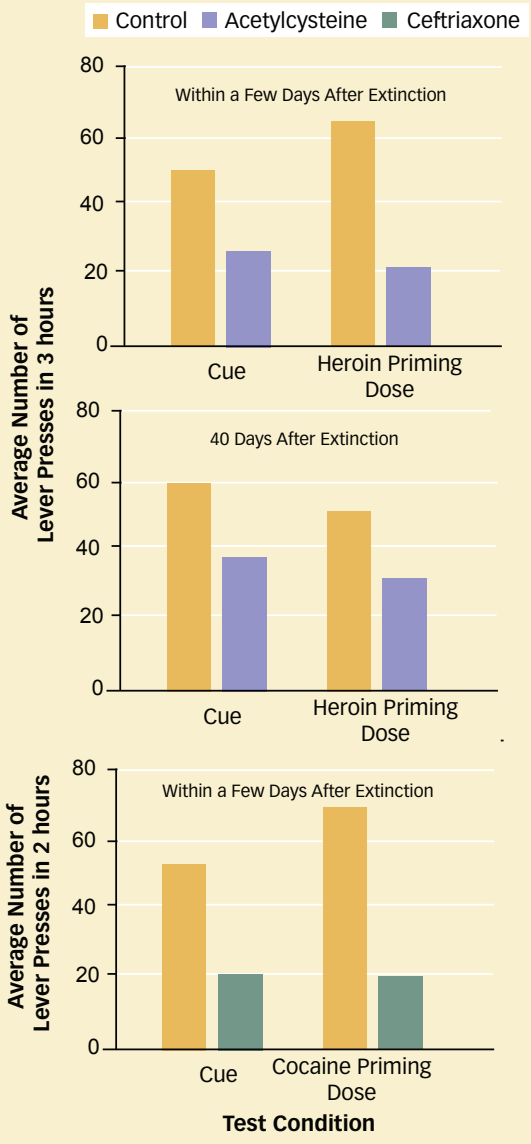
A MECHANISM CONFIRMED

The Kalivas group documented that, as they had predicted, xCT and GLT-1 levels were reduced in the brain tissue of experimental rats that had been exposed to heroin or cocaine, and these reductions could be reversed by treatment with acetylcysteine and ceftriaxone, respectively. The medications had no effect on those proteins in rats not exposed to drugs of abuse, suggesting acetylcysteine and ceftriaxone do not affect the glutamate balance in people who have not abused drugs.

A NIDA-funded study by Dr. George Rebec and colleagues at Indiana University yielded additional promising evidence. Following a self-administration and withdrawal protocol similar to that used by the Kalivas team, the Rebec team found that rats treated with ceftriaxone had GLT-1 levels that were twice as high in the nucleus accumbens (NAc) and three times as high in the prefrontal cortex (PFC) compared with those in rats that did not receive the medication. The increases correlated with reduced drug-seeking.

Recent experiments by Drs. Lori Knackstedt and Kalivas show that each medication influences both proteins. "Our results suggest that xCT and GLT-1 are inextricably linked and represent a

MEDICATIONS SHOW PROMISE AS RELAPSE PREVENTION THERAPIES Rats trained to self-administer heroin or cocaine by pressing a lever gradually stop seeking the drug (extinction of drug-seeking behavior) when lever-pressing no longer results in drug delivery. After a drug-related cue or an injection of a small priming dose of the drug, the rats again press the lever, in a model of addiction relapse. However, rats that received acetylcysteine or ceftriaxone while stopping showed less heroin- and cocaine-seeking, respectively, than control animals.



Glutamate Restoration Is Linchpin of Medications' Promise

In recent years, scientists have found that as occasional drug abuse evolves into addiction, and compulsion supplants pleasure as the primary motive for drug use, glutamate rather than dopamine becomes the neurotransmitter most closely tied to drug-seeking. Dr. Peter Kalivas and colleagues at the Medical University of South Carolina (MUSC) in Charleston were among the first to call attention to glutamate as a factor in addiction some 15 years ago.

Glutamate is the brain's primary excitatory neurotransmitter, and it participates in most aspects of normal brain function. The MUSC researchers observed that glutamate signaling in key brain areas is altered when rats self-administer drugs and then undergo withdrawal. Following up on these findings, the MUSC researchers showed that chronic drug exposure upsets the balance between glutamate used as a synaptic signal between neurons and glutamate used to signal between glia and neurons. The disturbance is greatest in a neural circuit that includes the prefrontal cortex (PFC) and the nucleus accumbens (NAc), areas that affect learning, memory, and reward-seeking.

The drug-induced perturbation of glutamate signaling induces a variety of neurobiological changes that appear to influence the transition from occasional drug abuse to addiction. These include:

- Alterations in the shape and density of the tiny knob-like structures, called dendritic spines, on which neurons receive neurotransmitter signals from other neurons;
- An increase in the abundance or activity of receptors that receive glutamate signals from other neurons;
- A decrease in a receptor that limits the amount of glutamate released as a signal;
- A decrease in receptors that control neurons' ability to alter the strength of their communication in response to experience—the basic molecular mechanism of learning.

Dr. Kalivas says that the alterations in neural activity resulting from glutamate imbalance limit a chronic drug user's ability to adapt to new information—for example, to stop taking drugs in the face of adverse consequences. "Drug-induced changes in glutamate distribution strengthen the power of learned associations surrounding drugs," he says. "These associations become so strong that they take over the addicted individual's world view, obscuring the pleasure and heightening the compulsion."

Experiments by Dr. Kalivas and colleagues have implicated glutamate imbalance in the hyperresponsiveness to drug cues that is a hallmark of addiction. They showed that drug cues prompt cells in the PFC to release a surge of glutamate into the NAc of a chronically drug-exposed animal. The NAc, which has reduced extracellular glutamate, responds with heightened intensity that may trigger drug-seeking.

"Dopamine triggers reward and is critical in the early stage of addiction, but glutamate is crucial in maintaining addiction and inducing its long-term effects," says Dr. Jerry Frankenheim of NIDA's Division of Basic Neuroscience and Behavioral Research. "However, the picture is quite complex. For example, dopamine and glutamate seem to modulate each other. NIDA is supporting several researchers who are examining the dopamine-glutamate relationship."

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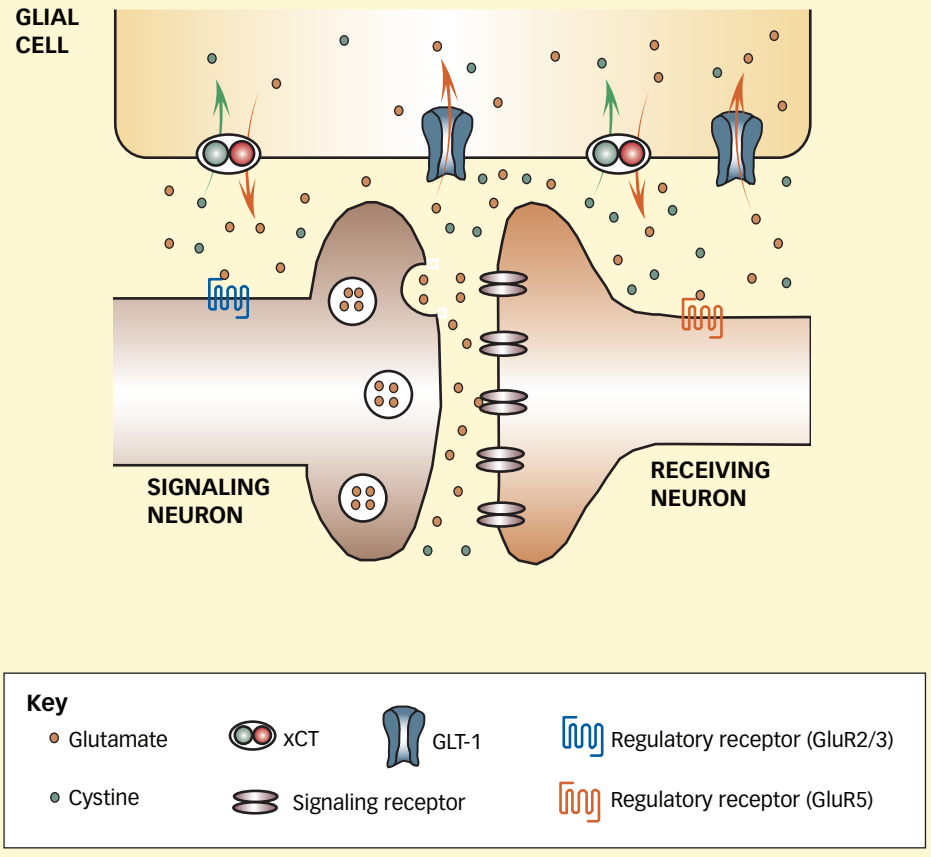
crucial component of the way the healthy brain maintains the glutamate balance," says Dr. Kalivas. The link supports the idea that restoring the glutamate balance—particularly in the pathway between the PFC and NAc—might normalize drug-induced changes in this neural circuit.

"The team's findings suggest that glutamate is a final common pathway for drugs of abuse and highlight the therapeutic potential of medications that influence this neurochemical," says Dr. Pilotte.

MEDICATIONS ENHANCE MEMBRANE PROTEINS THAT MAINTAIN GLUTAMATE BALANCE Extracellular concentrations of glutamate in the brain affect the neurochemical's release as a signal molecule and its effect on responding neurons. Extracellular glutamate is influenced by two proteins in the membranes of glial cells: xCT pushes glutamate out of glia as it brings in the amino acid cystine, and GLT-1 carries glutamate into glial cells. Chronic drug exposure and withdrawal decrease the abundance and activity of those proteins and disrupt glutamate balance. Acetylcysteine and ceftriaxone enhance the levels and activity of these proteins. The normalized glutamate balance that results also restores activity of glutamate receptors 2/3 and 5, which influence the release of glutamate from the sending neuron and regulate the long-term effect of the signal in the receiving neuron, respectively.



"These agents may help prevent relapse to many different drugs and, because glutamate does not drive the sensations of pleasure that underlie drug problems, they are likely to have low potential for abuse."

CLINICAL TRIALS

Encouraged by the results of their animal studies, Drs. Robert Malcolm, Steven LaRowe, and Kalivas conducted pilot clinical trials. In the first, 15 cocaine abusers reported less craving, reduced desire to use, and fewer responses to visual cocaine cues when taking the acetylcysteine than when receiving a placebo. In a second study, 16 outpatients reported smoking fewer cigarettes during a 4-week regimen of acetylcysteine than in the month before the treatment. Urine tests supported their self-reports.

Dr. Kalivas' team, with MUSC colleague Dr. Malcolm, has now begun a new study with more than 200 cocaine-addicted individuals. All participants are receiving cognitive-behavioral therapy; roughly two-thirds are also getting one of two doses of acetylcysteine and the remainder, a placebo.

If the medication is effective, fewer of those in the medicated groups will relapse during the 8-week trial.

"The results of the ongoing clinical trial will be of great interest because acetylcysteine is already used clinically, and it has a known safety profile," says Dr. Pilotte. "I think that this research is promising not only for the treatment of cocaine or heroin addiction, but also to reduce dependence on other stimulants, for example, amphetamine." ■

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Dr. Geoffrey Schoenbaum Receives the Waletzky Memorial Award

Dr. Geoffrey Schoenbaum, a professor in the department of anatomy and neurobiology and the department of psychiatry at the University of Maryland School of Medicine, is the recipient of the 2009 Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism. He accepted the award and delivered the keynote lecture at NIDA's "Frontiers in Addiction Research" miniconference in Chicago, Illinois, on October 16, 2009.

Dr. Schoenbaum's research demonstrates that exposure to abused drugs induces long-lasting changes to the brain's learning circuits, which can lead to a loss of control over behavior. His animal studies provide insight into why people addicted to drugs continue to abuse substances despite the negative consequences on health, relationships, and other aspects of life. Dr. Schoenbaum and colleagues combine sophisticated learning protocols and electrophysiology to examine drug-induced disruptions in the cellular processes underlying behavior regulation—particularly in the orbitofrontal cortex, a region of the brain that influences decisionmaking.

The $25,000 award is presented each year to a scientist who has received a doctoral degree within the past 15 years, and it is intended to reward and encourage innovative research into the neurobiology of drug addiction and alcoholism. The Waletzky family established the award in 2003 in memory of Jacob P. Waletzky, who died at age 29 of cocaine-induced cardiac arrhythmia.

NIDA Curriculum Piques Students' Interest in Addiction Careers

To fuel the future success of substance abuse research, young clinicians from diverse backgrounds need to be attracted to the field. As part of the national effort to draw health professionals to clinical substance abuse research, NIDA-supported researchers led by principal investigator Dr. Marc Gourevitch at New York University (NYU) developed the Substance Abuse Research Education and Training (SARET) curriculum. SARET comprises eight Web-based, interactive modules that introduce addiction research to graduate students of nursing, dentistry, and medicine. All three medical professions were included because they contribute to substance abuse research, clinical screening, and referral for substance abuse treatment. Students who complete the SARET curriculum may apply for stipend-supported training—lasting either a summer or a full year—with an addiction researcher on the NYU faculty. Student stipends are competitive with similar research stipends.

A recent pilot test of the first 30-minute curriculum module suggests that participating in SARET increases students' interest in addiction research, report Dr. Adina Kalet, the SARET Curriculum Director, and NYU colleagues. That module, called "Investigators Needed," features four filmed interviews with NIDA-funded investigators. In these films, the scientists discuss their research, highlight major areas of inquiry in addiction science, and present major principles of rigorous medical research.

Participants took surveys both before beginning the module and 6 weeks after completing it. Among the 376 second- and third-year dentistry students who completed the module, 277 responded to the followup online survey assessing their experience. Fifty-seven percent of the responders reported being "somewhat" or "very" interested in addiction research after participating in the module, compared with just 22 percent before the start of the pilot test. The students' behaviors also reflected interest in learning more about addiction research: 37 percent discussed the topics covered in online forums; 35 percent requested more information about SARET; and 60 percent requested additional information about the research presented.

Using the preliminary findings, Drs. Gourevitch and Kalet and colleagues will develop the remaining seven modules of the SARET curriculum. They plan to determine whether students who complete the first module continue with the curriculum and to evaluate whether those who enroll in SARET go on to participate in mentored research.

SOURCE

Kalet, A., Gillespie, C., Naegle, M.A., and More, F. Attracting health professional students to substance abuse research. *Medical Education* 43(11):1094, 2009.

French Government Honors Dr. Volkow

The French Institute of Health and Medical Research (INSERM) awarded its 2009 International Prize to NIDA Director Dr. Nora D. Volkow. The biomedical research organization recognized Dr. Volkow for her groundbreaking work demonstrating that drug addiction usurps the brain's reward circuitry and drives compulsive behaviors. A research psychiatrist and scientist specializing in neuroimaging, Dr. Volkow has served as NIDA's Director since 2003. INSERM honors researchers whose basic or clinical research has advanced

public health. INSERM selected seven award winners in 2009. Dr. Volkow accepted the award during a ceremony at the College of France learning center in Paris on December 17, 2009.

Four Scientists Receive Avant-Garde Awards

NIDA has selected four scientists for its 2009 Avant-Garde Award for HIV/AIDS research. The annual competition, now in its second year, is intended to stimulate groundbreaking research for the prevention and treatment of HIV/AIDS in drug abusers. Awardees receive $500,000 per year, plus associated facilities and administrative costs, for 5 years to support their research.

The four awardees and their proposed projects are:

- **Benjamin K. Chen, M.D., Ph.D.**, assistant professor in the Department of Infectious Diseases at Mount Sinai School of Medicine, New York, has developed an imaging method that enables in vivo visualization of fluorescently tagged HIV virus particles. By using this tool in mice in which the immune system has been altered to resemble that of people, Dr. Chen and colleagues will study the sequence of interactions between HIV-infected cells and uninfected cells. The team's goal is to answer long-standing questions about the mechanisms of viral transmission between cells and to provide strategies for development of vaccines or other therapies to inhibit these interactions.
- **Dana H. Gabuzda, M.D.**, is a professor of neurology at the Dana Farber Cancer Institute and Harvard Medical School in Boston. Dr. Gabuzda has conducted NIDA-supported studies on HIV pathogenesis and how substance abuse contributes to it. She now plans to investigate why only some HIV-infected individuals on antiretroviral drugs achieve long-lasting viral suppression and recovery of immune function, including normal numbers of CD4 T cells. The research proposed by Dr. Gabuzda aims to improve understanding of the mechanisms that determine CD4 T cell restoration in HIV-infected populations, including intravenous drug users, and thereby identify new therapies to restore immune function.
- **Jonathan Karn, Ph.D.**, is a professor and chairman of molecular biology and microbiology at Case Western Reserve University in Cleveland. Although most individuals treated with antiretroviral drugs have little to no detectable HIV in their blood, the virus has not necessarily been cleared from the body. The proposed research will focus on finding natural mechanisms that could provide long-lasting suppression of HIV replication to prevent renewed active infections if the virus re-emerges.
- **Rafick-Pierre Sekaly, Ph.D.**, co-director and scientific director of the Vaccine and Gene Therapy Institute in Port St. Lucie, Florida, studies human immunology, focusing on the immune response to HIV infection. Dr. Sekaly proposes to examine the HIV-1 reservoir, a small pool of long-lived, infected, immune system cells, and explore potential means to purge the virus from that hiding place. These studies could lead to novel immunological treatments that eradicate the HIV-1 reservoir and contribute to a cure for AIDS.

Further information on the Avant-Garde Award is available at *www.drugabuse.gov/about/organization/arp/AVGP.htm*.

Dr. Kathleen T. Brady Recognized

The Medical University of South Carolina (MUSC) Board of Trustees bestowed the title of Distinguished University Professor upon Dr. Kathleen T. Brady on February 12, 2010. A leader in addiction research, Dr. Brady has studied co-occurring substance abuse and mental health disorders and their treatment. Dr. Brady serves as Professor of Psychiatry and Behavioral Medicine at MUSC and graduated from its medical school.

With the Distinguished University Professor title—the highest academic honor granted by the university—the MUSC Board of Trustees recognizes scholars who are transformative leaders. Including Dr. Brady and the three other leaders inducted in 2010, only 32 individuals have received this MUSC designation.

Dr. Brady is the principal investigator and director of the Southern Consortium of the NIDA Clinical Trials Network, which tests substance abuse therapies in community-based treatment settings. She also serves as director of the South Carolina Clinical and Translational Research Institute, recipient of a 2009 National Institutes of Health Clinical and Translational Science Award. Dr. Brady is on the Editorial Board of *Addiction Science & Clinical Practice*, NIDA's peer-reviewed journal for drug abuse researchers and treatment providers. Her research focuses on victimization and post-traumatic stress disorder among substance users, with an emphasis on translating study findings into effective treatment interventions. ■

Adolescent Cigarette Smoking Holds at Lowest Recorded Levels

Cigarette smoking among adolescents in the 8th, 10th, and 12th grades has remained at the lowest levels recorded by the Monitoring the Future (MTF) survey since its inception 35 years ago. However, adolescents' use of smokeless tobacco increased significantly, to levels not seen since 2001. The 2009 MTF survey also found that use of illicit drugs, including marijuana, had not changed significantly since 2008. This adds to earlier evidence that the downward trend in teen marijuana use evident from the late 1990s through 2007 has stalled.

The prevalence of past-month cigarette smoking was 12.7 percent in 2009, a 55-percent decline from the peak years of 1996 and 1997, when 28.3 percent of adolescents reported smoking.

The prevalence of past-month smokeless tobacco use rose from 4.9 percent in 2008 to 6 percent in 2009. That rate had hovered around 5 percent since 2002. Even so, the 2009 rate is 38 percent lower than that of the peak years of the mid-1990s.

In 2007, abuse of methamphetamine had dropped to its lowest levels since the drug was added to the survey in 1999, and it remained at that low level in 2009. For example, among 12th-graders, past-month abuse rates fell from 1.7 percent in 1999 to 0.5 percent in 2009; past-year abuse rates dropped from 4.7 percent to 1.2 percent.

The MTF survey has documented a steady, long-term decrease in alcohol use, including binge drinking, across the three grades. However, only the 8th-graders showed a continuation of this decline in 2009. "They are the youngest and most vulnerable students in the survey, so that would be the place we would want to see the decline," says Dr. Marsha Lopez of NIDA's Division of Epidemiology, Services and Prevention Research.

AREAS OF CONCERN

The researchers assembled a list of the 13 drugs with the highest rates of abuse by 12th-graders. Eight of those drugs were prescription and over-the-counter medications. NIDA officials continued to express concern about the nonmedical use of prescription drugs, particularly opioid painkillers such as Vicodin and OxyContin. "These drugs are very potent, very addictive when not used as intended," says NIDA Director Dr. Nora D. Volkow. Abuse rates of prescription drugs have been steady since 2003 among the three grades surveyed, she adds.

In 2009, for the first time, the survey also queried students about nonmedical use of Adderall, a stimulant often prescribed to treat attention deficit hyperactivity disorder. Six percent of 10th-graders and 5 percent of 12th-graders said they had used the medication in the past year for purposes other than those for which it was prescribed.

PERCENTAGE OF STUDENTS REPORTING PAST-MONTH SUBSTANCE ABUSE*

	2001	2008	2009
Any illicit drug			
All grades	19.4	14.6	15.8
8th grade	11.7	7.6	8.1
10th grade	22.7	15.8	17.8
12th grade	25.7	22.3	23.3
Cigarettes			
All grades	20.2	12.6	12.7
8th grade	12.2	6.8	6.5
10th grade	21.3	12.3	13.1
12th grade	29.5	20.4	20.1
Marijuana			
All grades	16.6	12.5	13.8
8th grade	9.2	5.8	6.5
10th grade	19.8	13.8	15.9
12th grade	22.4	19.4	20.6
Alcohol			
All grades	35.5	28.1	28.4
8th grade	21.5	15.9	14.9
10th grade	39.0	28.8	30.4
12th grade	49.8	43.1	43.5

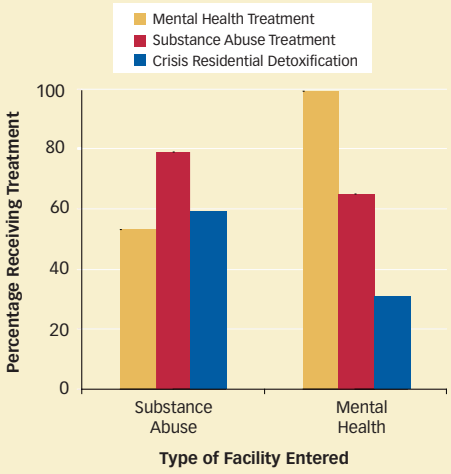
* In this table, none of the differences between 2008 and 2009 are statistically significant.

Ecstasy, LSD, and inhalants are also of concern because of a softening of perceived risk associated with their use over the past several years. Generally, abuse rates for these drugs have not increased in the past decade, but a decline in perceived risk is considered an early warning sign of an increase in the near future, notes Dr. Lloyd Johnston of the University of Michigan, lead investigator of the survey.

The 2009 survey covered 46,097 students in 389 public and private schools across the Nation. Participants reported their use of various substances in the past month, past year, and their lifetime as well as their attitudes about drugs and their perceptions of harmfulness, availability, and peer disapproval. Further information and the full text of the survey are available at *www.drugabuse.gov/drugpages/MTF.html* and at *www.monitoringthefuture.org*. ■

WHAT THE NUMBERS SAY

Treatment Patterns Vary Among People With Co-Occurring Disorders Based on Type of Treatment System Entered



A study followed individuals who entered mental health crisis or substance abuse detoxification residential centers in San Francisco. The groups entering each type of facility had similar, and similarly severe, co-occurring mental health and substance abuse disorders and might have been expected to require similar services post-crisis. Of 106 recruited at mental health crisis residential centers, 99 percent obtained further mental health treatment—and 65 percent were also treated for substance abuse—during the following 24 months. Of 118 recruited at substance abuse crisis detoxification residential centers, 53 percent received mental health services and 79 percent received post-crisis substance abuse treatment in the same period. The patients recruited at substance abuse centers were almost twice as likely to undergo crisis detoxification at a residential center during the followup.

Source: Havassy, B.E., Alvidrez, J., and Mericle, A.A. Disparities in use of mental health and substance abuse services by persons with co-occurring disorders. *Psychiatric Services* 60(2):217-223, 2009.

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